REMARKS

The Examiner states that Claims 1-43 are pending in this application. Claims 1-43 were previously cancelled. Claims 44-86 are currently pending. Page 2 of the Office Action states that restriction to one of the following inventions is required under 35 U.S.C. 121 and 372:

I. Claims 1-10 (now claims 44-53), drawn to an agent for inhibiting the release, maturation and replication of members of the Flaviviridae family

II. Claims 11-17 (now claims 54-60), 29-43 (currently Claims 72-86) drawn to the use of proteasome inhibitors for inhibiting the entry/internalization process, replication, maturation and infection of Flaviviridae.

III. Claims 18-28 (now claims 61-71) drawn to the use of proteasome inhibitors for inducing the death of hepatocarcinoma cells and preventing the development of liver cell carcinomas.

Applicants have amended claims 54-60 and 72-86. Claims 54-60 and 72-86, as amended, are now method claims that employ the composition of claims 44 and 50. In an attempt to advance the prosecution of the subject application, but without conceding the correctness of the Examiner's position, applicants have elected the claims in Group I with traverse, which include claims 44-53, as well as the amended claims 54-60 and 72-86 for purposes of prosecution.

Applicants note that the Xu reference ("Hepatitis C Virus F Protein is a Short-Lived Protein Associated with the Endoplasmic Reticulum," Journal of Virology, Vol. 77, No. 2, Jan. 2003, pp. 1578-1583) does not disclose agents for inhibiting the release, maturation and replication of Flavivirus or Pestivirus. The examiner alleges that this work reports that half live

of the HCV protein F can be increased by proteasome inhibitors. However, from this observation applicant respectfully submits that no one of ordinary skill in the art would conclude that this effect, e.g. the stabilization of protein F by proteasome inhibition, has any deleterious effect on the release, maturation, and replication of members of the Flaviviridae family. On the contrary, in this publication it is clearly stated that the F-protein is localized to the endoplasmic reticulum and may participate in the replication machinery of HCV. Thus, if the F protein fulfills an critical function in HCV replication, one must conclude that this function is even more pronounced if the expression level of the protein F in an HCV infected cell is enhanced. In other words, the publication cited by the reviewer implies that proteasome inhibitors support, rather than suppress, the HCV replication. Consequently, Xu et al. does not support the conclusion that using proteasome inhibitors for treating HCV infection was known in the prior art.

The prior art is directed to the HCV. However, applicant respectfully submits that one of ordinary skill in the art would not conclude based on the prior art that the effect of proteasome inhibitors on HCV can be generalized to Flavivirus or Pestivirus, which belong to different genera of viruses. Furthermore, applicant respectfully submits that all experiments reported by Xu et al. are conducted from transgenes expressing solely the protein F, not a single experiment was preformed in the background of the replicating virus system, even though cell culture systems suited to test the effect of the protein F on the replication machinery has been known. Thus, there are no data in Xu et al. providing any evidence to one of ordinary skill in the art that proteasome inhibitors interfere with Flavivirus or Pestivirus replication or morphogenesis.

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CONCLUSION

Applicant respectfully submits that this application is in condition for allowance. Early and favorable action is earnestly solicited. No fee, except for the fee in connection with the one month extension fee, is believed due in connection with the filing of this Response However, if any additional fee is due the amount of such fee may be charged to Deposit Account No. 19-4709. In the event that there are any questions, or should additional information be required, please contact applicants' attorney at the number listed below.

Respectfully submitted,

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